Page 9, line 22, replace "requires" with –has-.

Page 9, line 24, replace "the" with –than-.

Page 9, line 25, replace "required" with –require-.

Page 9, line 30, replace "cause" with –caused-.

Page 10, line 28, delete "as".

Page 10, line 30, replace "depo" with –depot-.

In The Drawings

Submitted herewith please find a proposed correction of Fig. 1 with the proposed correction indicated in red on a copy of Fig. 1 as filed. The correction of the symbols in the Figure key do not present new subject matter and should be allowed.

REMARKS

Claims 1-3 (in part), 5-6, 7-11 (in part), and 22-25 are currently pending in the application.

The Subject Matter of the Pending Claims is Non-Obvious In View Of Bechgaard

All pending claims are rejected as obvious and therefore unpatentable over Bechgaard et al. (US Patent No. 5,397,771). Applicant traverses the rejection and requests reconsideration and allowance.

Claim 1 is directed to a formulation that is specifically well-suited for simultaneously achieving several important objectives: [1] permitting subcutaneous delivery of [2] a lipophilic agent in a physiologically well-tolerated oil and benzyl

alcohol formulation which permits [3] peak plasma concentration to be reached over a period of up to 4 hours and [4] achieves sustained delivery.

According to section 2142 of the Manual of Patent Examining Procedure (MPEP),

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Claim 1, and those claims dependent from it (the remarks should be viewed as applying equally to those claims not dependent from claim 1), have been rejected as obvious in view of Bechgaard which discloses a formulation [1] that *requires n-glycofurol* (**optionally** in combination with water or oil); [2] is explicitly designed for immediate (<20 minutes, Col. 2, line 18-24) and short term nasal delivery; and [3] is explicitly designed to be needle-less. In contrast, Applicant's claimed invention does not require n-glycofurol, is not limited to Bechgaard's 20 minute window, is not short term, is not designed to adsorb via nasal mucosa, and contains benzyl alcohol for reducing variability between individuals. With reference to MPEP section 2142, the Examiner has not demonstrated where Bechgaard suggests or motivates one to use or modify his teachings for preparing a subcutaneous dosage form. Why would one remove n-glycofurol from Bechgaard's formulation? Why, in spite of Bechgaard's teaching at Column 1, lines 18-23 about his aversion to needles, would one consider putting his formulation under the skin through a needle? How can one call obvious a jump from a statement in Col. 10, lines 21-23 regarding optimizing bioadhesion, sprayability or

viscosity, for turning a needle-less, immediate release, cross-mucosal, n-glycofurol containing nasal administration formulation to a subcutaneous, sustained release formulation having no n-glycofurol? Why would anyone reading Bechgaard have any reason to believe or expect that using his formulation in a subcutaneous administration would provide the results shown by the Applicants.

Bechgaard does not answer any of these questions and neither has the outstanding Office Action, thereby failing to make a case for obviousness.

The present application teaches an injectable formulation designed to be optimally suitable for rapid drug uptake in the unique microanatomy of the subcutaneous environment. Bechgaard et. al. teaches a method of drug delivery optimized to transverse various mucosal membranes, including oral,vaginal and rectal mucosa. Contrary to the implication in Bechgaard that his formulations can be used for parenteral administration as well as for nasal administration, one of skill in the art knows that one does not inject oils and polyethylene glycol directly into the bloodstream, yet these, and n-glycofurol in particular, are aspects of Bechgaard's nasal formulations.

The constituents of the formulation of Bechgaard et. al. comprise various mixtures and solutions involving various ethylene glycols in combination with vegetable oils as well as oil-to-water emulsions in combination with various ethylene glycols, including polyethylene glycol (PEG) and n-glycofurol in order to maximize rapid transmucosal uptake of the various active ingredients cited. Such mixtures, if delivered to the subcutaneous microanatomy of readily accessible capillaries which include both vessels and lymphatics, would be expected to actually slow the rate of uptake of the active ingredient rather than accelerate it (the opposite of Bechgaard's intentions).

Therefore, the skilled artisan would not naturally consider a parenteral route of administration, much less a subcutaneous route administration.

Bechgaard identifies two major problems which he seeks to address: [a] a need to get away from needles (Col. 1, lines 11-23); and [b] an overriding need to avoid mucociliary clearance by either rapid (<20 minutes, *Id.*) absorption across the mucous membrane or enhancing the mechanical stickiness of his formulation to slow down the effects of mucociliary clearance (hence the reference to ethoxylated castor oil in Col. 10, line 46, which will be further discussed hereinbelow). Both of these points teach in the completely opposite direction of the present invention.

Bechgaard's emphasis on rapid absorption is diametrically opposed to the requirements of claim 1 of peak plasma concentration being reached over a period of up to 4 hours. Bechgaard even identifies as prior art Lau and Slattery's efforts to deliver diazepam and lorazepam via nasal administration in a polyethoxylated castor oil (Col. 2, lines 32-47) and characterizes [i] the 1.4 and 2.3 hour time periods to reach peak plasma concentrations and [ii] the absolute plasma levels reached as unsatisfactory compared with intravenous administration. Bechgaard did not observe that Lau and Slattery might be useful for subcutaneous administration because he did not recognize that fact and thus could not be said to make obvious such a suggestion.

Another point to be made here relates to the Examiner's reliance on Bechgaard's use of ethoxylated castor oil "for designing a controlled-release formulation...which **avoids** peak plasma concentrations" (Col. 10, lines 47-49, emphasis supplied). Firstly, the present invention does not seek to avoid peak plasma concentration. Secondly, Bechgaard does not teach in any way how one is supposed to make a controlled release

using ethoxylated castor oil. Thirdly, to avoid the apparent internal inconsistency of supposedly teaching rapid absorption, immediate release nasal administration together with controlled release formulations it is clear that we must undertstand Bechgaard's reference to "controlled release" as implying that sticky ethoxylated castor oil can be used to increase the time which the formulation spends in the sinus passages before being mechanically cleared. This interpretation is clearly correct when one takes into account the reference at Col. 10, lines 21-23 to optimizing bioadhesion and viscosity (not jumping from nasal to subcutaneous as the Examiner argues). Furthermore, controlled release which avoids peak plasma levels implies a zero order release rate, i.e. one where the entry of the active ingredient into the plasma is at a constant rate. By contrast, sustained release refers to prolongation of an active's entry into the plasma. Although the ethoxylated castor oil may permit a longer period of mechanical contact and adsorption by resisting mucociliary clearance, its zero order release profile would not be thought of as sustained release in the traditional sense. In the context of the present invention, it is understood that sustained release refers to the relatively level and slowly tapering off plateau which follows the first spike in plasma levels after administration.

Nasal administration and injectable formulations are not obvious in view of one another and cannot be used to make a prima facie case of obviousness in view of one another absent a specific reference which equates the two methods. To equate these methods is like equating transdermal drug delivery with parenteral delivery, i.e. not reasonable. Although thin, the mucosal epithelium still serves as an effective safety barrier which is not present for i.v., i.m., and subcutaneous injection (see Col. 1, lines 52-53). In view of this fact, there are many nasal formulations which use excipients which

could never be parenterally administered into a patient. Additionally, what works in the arena of injectable formulation does not necessarily satisfy the needs of nasal dosage form formulators.

Bechgaard's simple observation that his formulation may be administered intravenously can not be taken to indicate that he appreciated the particular and surprising suitability for rapid but sustained release which is afforded by the subcutaneous administration of an oil and benzyl alcohol formulation comprising lipophilic agents. This is especially so since Bechgaard himself disparaged intravenous injection and sought to do away with parenteral administration of all kinds as much as possible.

Bechgaard does recite benzyl alcohol, at Col. 10, line 63-64. However, he does not teach what he uses it for, he simply says it can be used if one wants to. But there is no teaching as to why one would want to. Bechgaard certainly does not suggest or motivate one to even explore the possibility of using benzyl alcohol beyond merely naming it as something that won't hurt. There is no reference whatsoever of the unique property which benzyl alcohol (and possibly other closely related alcohols) may have in the context of subcutaneous delivery of lipophilic agents of reducing variability in time to peak and plasma levels at peak between subjects.

From the discussion above, it is clear that the only thing that should be obvious from Bechgaard, is that Bechgaard makes nothing obvious in the art of subcutaneous, sustained release administration.

In summary, the presently claimed invention requires subcutaneous administration of the lipophilic agent diazepam, in an oil vehicle, in the presence of benzyl alcohol, to achieve a peak plasma concentration within 4 hours and to achieve a

sustained delivery. In contrast, the cited prior art, Bechgaard et al, requires n-glycofurol and discloses only i.v. and nasal administration, and specifically claims only nasal mucosal administration with peak plasma concentration achieved within minutes. Therefore, the prior art does not disclose many elements of the presently claimed invention, including subcutaneous administration and sustained delivery.

There is no suggestion that changing the route of administration to subcutaneous delivery achieves any of the goals achieved by the present invention, and no showing has been made that it would have been obvious to one having ordinary skill in the art to do so. Therefore, Applicant respectfully submits that the Office Action does not establish a *prima facie* case of obviousness.

In the event that the present Response is not deemed to put the application in condition for allowance, Applicant further requests the withdrawal of the holding of the most recent Office Action as Final. In view of the confused circumstances surrounding the restriction requirement, acknowledged by the Examiner in the latest Office Action, it is not clear that the first substantive Office Action fairly reflected a proper consideration of the claims which Applicant intended to be before the Examiner. Hence, in effect, the confusion may have prevented the Response from properly being able to address those issues which the Examiner found troubling. Applicant has a right to make at least one Response to a properly framed Office Action before receiving a Final rejection, and it is Applicant's view that this most recent Office Action and Response are the first exchange of papers where Examiner and Applicant are focusing on the same claims, a condition not of Applicant's making. Therefore, it is deemed proper that the Examiner withdraw his

holding as Final the August 23rd, 2002 Office Action and permit Applicant one more response should the claims not be allowed.

Miscellaneous Matters

The Applicant has taken this opportunity to make minor amendments, mostly in the nature of typographical errors. Applicant has also noticed an inadvertent mislabeling in the legends used in association with Fig. 1 and has submitted a proposed correction of the drawing and amended the specification to reflect the correction. No new subject mater has been added by virtue of this amendment. This is particularly so in that the two mislabeled curves of Fig. 1 were derived from a drawing which is part of the PDR monograph for Diastat (a suppository formulation for diazepam). A copy of the relevant portion of the monograph is submitted herewith for review. As such, the i.v and Diastat curves were known and the correction of the labeling is not new subject matter. Upon acknowledgement by the Examiner that the proposed correction is acceptable, a corrected Formal Drawing will be submitted.

Additionally, Applicant submits herewith a formal **CORRECTION OF TYPOGRAPHICAL ERROR IN SPELLING OF INVENTOR'S NAME** to delete the middle initial "D" and requests the issuance of a corrected Filing Receipt.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

Since this Response is in answer to a Final Office Action, a courtesy copy of this Response is being simultaneously transmitted to the Examiner's Technology Center 1600 at 713-308-4556. Applicant respectfully urges the Examiner to accept a phone interview should continued rejection be contemplated. Applicant will contact the Examiner for the purpose of arranging such an interview within the week following the filing of this Response.

It is believed that no extension of time is needed; however, if an extension is required, this conditional petition for an extension of time is being made in the event that the need for an extension has been overlooked. Please charge deposit account number 19-4972 for any additional fees that may be required for the timely consideration of this application.

Date: October 23, 2002

Respectfully submitted,

Morton Chirnomas
Registration No. 34,465
Attorney for Applicants

Bromberg & Sunstein LLP
125 Summer Street
Boston, Massachusetts 02110-1618
Tel: (617) 443-9292
Fax: (617) 443-0004

01540/00140 223318.1